REMARKS

Claims 1-19 and 24 are currently pending. Applicants have withdrawn claims 20-23, and cancelled claim 10 without prejudice or disclaimer of any of the subject matter contained therein. Accordingly, claims 1-9, 11-19 and 24 remain in the application.

Applicants have amended the dependency of the previously presented claims 9 and 14. Support for the amendments is found throughout the specification, specifically at page 2 lines 25-26 for claim 9 and at page 2 lines 28-31 for claim 14. Applicants have also amended claim 24 in light of the fact that claim 10 is cancelled. Applicants respectfully request entry of the amendments and submit that no new matter is added.

Applicants also thank the Examiner for pointing out the informalities present in claims 2 and 9. As such, Applicants have amended claims 2 and 9, such that claim 2 now ends with a period and claim 9 has a space between "Claim" and "2". In addition the Examiner has rejected claim 11 under 35 U.S.C. § 112, second paragraph; claims 1-19 under 35 U.S.C. § 102(b) and claims 1-19 and 24 under 35 U.S.C. § 103(a). These rejections are discussed in detail below.

In view of the amendments and remarks presented herein, reconsideration of the present application is respectfully requested.

REJECTION OF CLAIM 11 UNDER 35 U.S.C. § 112

Claim 11 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that claim 11 is confusing in that it depends on claim 9 which is not drawn to a lyophilized composition but requires a reconstitution diluent. Applicants have amended claim 9 to depend from claim 2 instead of claim 1. Therefore, claim 11 now depends on claim 9 which is drawn to a lyophilized composition. Applicants accordingly request withdrawal of the rejection.

REJECTION OF CLAIMS 1-19 UNDER 35 U.S.C. § 102 (b) IN VIEW OF CARLSON ET AL.

Claims 1-19 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Carlson et al., U.S. Patent No. 6,159,468 (Carlson et al.). The Examiner states that that Carlson et al. teach a composition comprising human protein C, 0.4M sodium chloride, and

20mM Tris-acetate, pH 6.5 (Preparation 1); Preparation 1 is made 5mM in EDTA and passed over a thrombin column, thus activating protein C, and eluted with Tris buffer and lyophilized (Preparation 2). Preparation 2 therefore comprises activated protein C, EDTA (a chelator; see column 7, lines 1-2), Tris-acetate, and sodium chloride at pH 6.5 (column 7, lines 26-27; Example 1).

Applicants respectfully remind the Examiner, that "a claim is anticipated only if each and every element as set forth in the claim is found either expressly or inherently described in a single prior art reference." *Verdegaal Bros. V. Union Oil of Cal.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The composition that the Examiner is referring to in the Carlson et al does not teach a pharmaceutical composition of activated protein C (aPC) and a chelating agent. Even if the Examiner is correct with respect to Carlson et al. disclosing a protein C zymogen preparation (Preparation 1) containing EDTA being subsequently passed over a thrombin column (column 7 lines 1-2), the resulting effluent in the process not only contains activated protein C, EDTA, buffer and salt, *but also leached thrombin from the column* (column 7, line 17). One skilled in the art would certainly understand that leached thrombin is not acceptable for pharmaceutical administration to humans. Applicants point out that each claim is directed to pharmaceutical compositions, including the preparation and use of these claimed pharmaceutical compositions.

In addition, the Examiner alleges that Preparation 2 contains aPC, EDTA, Tris-acetate and NaCl at pH (column 7, lines 26-27) and it is this preparation that is lyophilized and formulated (Examples 1and 2). Applicants point out that the Examiner has misunderstood the purification process described in Carlson et al. since Preparation 2 does not contain EDTA. Carlson et al. elaborates that the mixture containing the leached thrombin, aPC and EDTA discussed above is further passed thru an anion exchange column (Column 7, lines 17-19) to eliminate impurities. While the aPC binds to the anion exchange resin, the mixture containing the leached thrombin and EDTA passes through the column and are discarded. The bound aPC is subsequently washed with 20mM of a equilibration buffer (either 20mM Tris-acetate, pH 6.5 or 20mM Tris, pH 7.4) and finally eluted using 0.4 M NaCl in either Tris-acetate, pH 6.5 or 20mM Tris, pH 7.4 (Column 7 lines 17-27). This preparation (Preparation 2) in contrast to the Examiner's statement does not contain EDTA. Therefore, the lyophilized product of Preparation 2 and the formulations taught in Examples 1 and 2 of Carlson et al. do not disclose a pharmaceutical composition containing EDTA.

To be anticipatory, "The identical invention must be shown in as complete detail as is contained in the ...claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1013, 1920 (Fed. Cir. 1989). Carlson et al. does not teach or suggest a pharmaceutical composition of activated protein C (aPC) and a chelating agent. Therefore, Carlson et al. does not anticipate the Applicants' claimed invention and withdrawal of this rejection is requested.

REJECTION OF CLAIMS 1, 9 and 11-13 UNDER 35 U.S.C. § 102(b) IN VIEW OF FOSTER ET AL.

Claims 1, 9, and 11-13 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Foster et al., U.S. Patent No. 5,516,650 ('650) taken in light of Carlson et al. The Examiner states that '650 patent teaches a solution comprising activated protein C, EDTA (a chelating agent), and TBS (Tris-buffered saline) in water (column 21, lines 20-24). Carlson et al. is cited as evidence that Tris is a pharmaceutically acceptable buffer (column 3, lines 9-12).

Applicants point out that they discovered that the addition of a chelating agent to the diluent used with the aPC formulation or to the aPC formulation itself improves the solution stability of aPC. Foster *et al.* on the other hand, teaches a method of purifying a variant form of activated protein C that encodes a cleavage site sequence constructed by mutagenesis (column 19 lines 55-61). The '650 patent states that this variant activated protein C can be purified from media using a monoclonal antibody column specific for calcium-induced conformation of protein C, and subsequently eluted using TBS containing EDTA. The EDTA in the elution buffer is used to chelate metal ions and prevent the specific monoclonal antibody in the column from binding to Protein C (column 9 lines 44-48). The monoclonal antibody in the column only recognizes and binds calcium-induced conformation of Protein C and not Protein C without calcium-induced conformation. Therefore, the efficient way to elute the protein is by binding all the calcium with the EDTA during elution. Nowhere does Foster *et al.* teach or suggest that the EDTA could be used in an aPC formulation or that the eluent from the antibody column could be used as a pharmaceutical composition. Instead, Foster *et al.* recognized that additional purification of this eluent would be required. This is evident from the disclosure at column 9 lines 48-50 which stated that "[a]dditional purification of the column eluate may be achieved by conventional chemical purification means." Moreover, a person skilled in the art would certainly understand that

this eluent from the monoclonal antibody purification column would not be acceptable for pharmaceutical administration to humans.

Therefore, the pharmaceutical compositions of the present invention were not disclosed or suggested by Foster *et al.*

REJECTION OF CLAIMS 1-19 and 24 UNDER 35 U.S.C. § 103(a) IN VIEW OF CARLSON ET AL.

Applicants thank the Examiner for the reminder to consider inventorship in light of 37 C.F.R. § 1.56. The subject matter of the various claims was commonly owned at the time the invention covered herein were made, therefore, no amendment is necessary at this time.

Claims 1-19 and 24 are also rejected under 35 U.S.C § 103(a) as being unpatentable over Carlson et al. Applicants traverse this rejection. As stated in the discussion above, in contrast to the Examiner's statement Preparation 2 in the '468 patent does not contain any EDTA. Moreover, the lyophilized product of Preparation 2 and the formulations taught in Examples 1 and 2 of Carlson et al. do not contain any EDTA. Therefore, Carlson et al. does not teach or suggest all the limitations of Applicants' claims directed to a pharmaceutical composition comprising activated protein C and a chelating agent.

The Examiner further alleges that while the composition of Carlson et al. comprises some EDTA from the activation step (column 7, lines 1-3), a person of ordinary skill in the art would have had a reasonable expectation of success in including additional EDTA in the composition of Carlson et al. because EDTA is taught by Carlson et al. not to affect the composition's essential properties. The skilled artisan would have been motivated to include additional EDTA for the expected benefit that activated protein C would be protected from calcium and other divalent ions.

The inquiries for determining obviousness under Section 103 are: (1) Determine the scope and the contents of the prior art; (2) Ascertain the differences between the prior art and the claims at issue; and (3) Resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere*, 148 U.S.P.Q. 459 (1966). The PTO bears the initial burden of establishing a *prima facie* case. *In re Piasecki*, 745 F.2d 1468, 1472, 223 U.S.P.Q. 785, 787-88 (Fed. Cir.1984). To establish a *prima facie* case, the Examiner must show (1) some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); (2) the proposed modification of the prior art must have had a reasonable expectation of success,

determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200,1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991); and (3) the prior art reference or combination of references must teach or suggest all the limitations of the claims and all such teachings, as well as the expectation of success must come from the prior art, not Applicants disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir.1991). Applicants respectfully assert that the Examiner has failed to set forth a *prima* facie case of obviousness.

There has been no evidence that the skilled artisan would have been motivated to modify the cited prior art reference or more importantly that Applicants' modifications would have a reasonable expectation of success. Applicants submit that the Examiner has failed to set forth a prima facie case.

In order to further prosecution, Applicants point out that they discovered that the addition of a chelating agent to the diluent used with the aPC formulation or to the aPC formulation itself improves the solution stability of aPC. The chelating agents provide a means for sequestering metals that would otherwise promote aPC degradation resulting in the less active 1-149 light chain variant. Carlson et al. fails to teach the effect that metal ions or chelating agents may have on the propensity of activated protein C to form truncated variants or on its stability. At most it provides a method to effectively sequester metals such that they don't interfere with thrombin and its ability to effectively cleave Protein C zymogen. The Examiner identifies no suggestion or incentive in Carlson et al. that would have motivated the skilled artisan to protein C to add a chelating agent to the diluent used with the aPC formulation or to the aPC formulation itself to improve the solution stability of aPC. Therefore, the skilled artisan would not have been motivated to modify the cited prior art reference or more importantly have a reasonable expectation of success

If the Examiner persists in this rejection, Applicants respectfully request that the Examiner substantiate this allegation with sound reasoning or evidence. Withdrawal of this rejection is respectfully requested.

CONCLUSION

Having addressed all outstanding issues, Applicants respectfully request entry and consideration of the foregoing amendments that place the application in condition for

allowance. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

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